REMARKS

Claim 1-39 are pending and stand rejected prior to entry of the above amendments to claims 1, 6, 16, 21 and 34, as well as the cancellation of claim 13. New claims 40 and 41 have also been added with this action. Following entry of these changes, claims 1-12 and 14-41 will be pending. The amendments to claims 1, 6, 16, 21 and 34 were made for the sake of clarity and to expedite prosecution. Support for these amendments and new claims 40 and 41 can be found in the original claims as filed as well as throughout the specification. These amendments add no new matter. Applicants reserve the right to pursue unclaimed subject matter at a later date.

Priority

The Office Action states that Applicant has not complied with rules 37 CFR 1.78(a)(2) and (a)(5) for receiving the benefit of an earlier filing date under 35 U.S.C. § 120. Accordingly, Applicants have amended the specification by adding a first sentence that makes specific reference to the prior application from which priority is claimed.

Rejection under 35 U.S.C. §112, 2nd paragraph

Claims 1-7, 14-22, and 29-39 have been rejected under 35 U.S.C. §112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, with regard to claim 1, the Office Action states that 'it is unclear whether the phrase "set forth as SEQ ID NO: 5' refers to the conserved gag region or its complement."

Accordingly, Applicants have amended claims 1 and 16 to clarify that the claimed sequence set forth as SEQ ID NO:5 is an antisense sequence that is complementary to nucleotides 324 to 345 of a conserved *gag* region of the HIV-1 genome. Reconsideration and removal of this rejection is therefore respectfully requested.

Claims 16-30 and 34-36 have been rejected under 35 U.S.C. §112, second paragraph, as "being incomplete for omitting steps." In particular, the Office Action states that "No positive step is recited in the claims," and that this omission amounts to "a gap between the steps."

Accordingly, Applicants have amended claims 16 and 34 to clarify that the claim recites a positive step, namely that of "administering to the mammal" and "contacting the cell" respectively for claims 16 and 34. Applicants have also made further amendments to clarify that the claimed method "thereby treat(s)" and "thereby inhibit(s)" for claims 16 and 34 respectively. Reconsideration and removal of this rejection is therefore respectfully requested.

The Office Action further states that "the metes and bounds of an oligonucleotide 'specifically complementary' to nucleotides 324 to 345 of gag, in claim 1, line 2, and in claim 16, lines 6-7, cannot be determined."

Applicants respectfully submit that the above amendment relating to the complementarity of particular claimed sequences to the conserved region of *gag* obviates this rejection. Reconsideration and removal of this rejection is therefore respectfully requested.

The Office Action further states that the phrase "four 3'-terminal ribonucleotides" appears twice in claim 6 at lines 2-3. Accordingly, claim 6 has been amended to correct this obvious typographical error and to reflect the fact that the claimed oligonucleotide has both "four 3'-terminal ribonucleotides and four 5'-terminal ribonucleotides." Claim 6 has been further amended to reflect the claimed "oligonucleotide of claim 2," rather than "method of claim 2." Reconsideration and removal of the rejection is therefore respectfully requested.

Rejection under 35 U.S.C. §112, 1st paragraph (enablement)

Claims 16-30 have been rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for a method of treating HIV-1 or HIV-2 infection in a mammalian cell in vitro comprising the administration of SEQ ID NOs: 1-5, does not reasonably provide enablement fro a method of inhibiting proliferation of HIV-1 or HIV-2 in a mammal..." (emphasis added).

Applicants respectfully traverse this rejection for the reasons that follow.

First, the claimed invention is enabled because it is neither overly broad in scope, nor requires undue experimentation. In applying the *Wands* factors to as assessment of enablement

of the instant claimed invention, the Office Action states that "(t)he breadth of the claims is very broad...(and that)...the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and/or tissues harboring HIV1 or HIV2 in an organism whereby viral proliferation is inhibited *in vivo*...".

Applicants respectfully note that, not only is the breadth of the claims in the instant application not very broad at all, but also that the amount of experimentation required is not undue. Indeed, the claimed invention in dispute is limited to methods of treating HIV using an antisense oligonucleotides having only a few different nucleotide sequences (*e.g.*, the possible 21 mer sequences within the 22mer sequence specified by SEQ ID NO: 5 including SEQ ID NOs.: 1, 2, 3 and 4 (in claim16, as amended)). Furthermore, such sequences have been shown to be effective in blocking and treating HIV-1 infection in MT-4 cells (see, *e.g.*, Figures 1-3 which show the efficacy of "GEM® 92" (*i.e.*, SEQ ID NO: 1) as well as, subsequently, in whole organisms as discussed further below (see Exhibits B and C). Accordingly, there is also no "undue experimentation" in using the claimed methods. Therefore both the breadth of the claims and the quantity of experimentation required supports enablement of the method of the invention.

Second, the Office Action states, in further applying the *Wands* factors to an assessment of enablement of the claimed invention, that "the *in vivo* (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues," citing Branch ((1998) TIBS 23: 45-50) and Crooke (1998) Antisense Research and Application pp. 1-49). The Office Action further states that "(t)he high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment."

Applicants note that the claimed invention in this case has overcome the cited unpredictability in the art. Indeed the cited problem of "target accessibility" has been overcome, as evidenced by the support in the specification showing efficacious anti-HIV effects of the

claimed antisense in infected MT-4 cells, while the cited issue of "delivery" is not problematic as evidenced by the *in vivo* studies cited above and discussed further below. Furthermore, while there may be individual and specific instances of failure that support the assertion that the use of antisense *in vivo* "is a highly unpredictable endeavor due to target accessibility and delivery issues," they are not determinative of enablement of the instant claimed invention. In particular, Applicants respectfully note that an isolated statistical failure, in a phase III clinical trial required for FDA approval, does not defeat patentability for lack of enablement because the standards applied for FDA approval are not those required for patentability. The Federal Circuit has stated that "considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled" (citing *Scott v. Finney*, 34 F.3d (Fed. Cir. 1994), at MPEP 2164.05). Moreover, the cited negative report, published in 1999, is contradicted by subsequent phase II clinical trial results, which demonstrated "significant and long-lasting improvement of symptoms in patients with ulcerative colitis" (see Exhibit A).

Still further, Applicants respectfully note that the reasoning of the rejection is inconsistent, inasmuch as the cited results are for a different antisense oligonucleotide that targets a different mRNA for use in treating a different disease. Even if the cited anti-ICAM-1 antisense did fail, it would not negate patentability of the instant anti-HIV antisense oligonucleotides. Furthermore, the failure of one individual antisense oligonucleotide does not logically support lack of enablement of completely unrelated antisense oligonucleotides with different targets and disease indications. Indeed, while Applicants can cite numerous instances of success with unrelated antisense oligonucleotides that have been shown to be effective *in vivo*, it is the success of the claimed anti-HIV antisense oligonucleotides that is most relevant to the question of enablement in this case.

The success of anti-HIV antisense oligos related to the instant claimed invention is evident from the results of numerous *in vivo* studies which follow the teachings of the specification, which are discussed further below. For example, an initial single dose phase 1 study of GEM®92, corresponding to SEQ ID NO:1 of the instant invention, administered orally at three dose levels as well as by injection showed excellent safety results and demonstrated effective oral delivery in humans of these 2nd generation antisense agents (see Exhibit B, page 2

from Applicants website at www.hybridon.com/drugdevelop/ clinical_program). Furthermore, Applicants' previous anti-HIV antisense treatment, GEM®91, which corresponds to a 25-mer phosphorothioate oligonucleotide that targets the same *gag* sequence as the instantly claimed antisense oligonucleotides "significantly reduced viremia in HIV-positive patients treated for up to eight days" (see Exhibit C). As discussed above, although concerns regarding the safety of GEM®91 may hinder FDA approval or further commercial development of this 25mer, they do not negate patentability of the instant related antisense technology.

Finally, the Office Action states, in still further applying the *Wands* factors to an assessment of enablement of the instant claimed invention, that "Applicants have not provided guidance in the specification toward a method of treating or inhibiting proliferation of HIV1 or HIV2 in a mammal (by) administration of a 21 nucleobase oligonucleotide that specifically targets nucleotides 324 to 345 of the gag region of HIV1." Further on this point, the Office Action states that the specification "fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery, inhibition of HIV1 or HIV2 proliferation or treatment effects provided in an organism using antisense." Applicants respectfully disagree and point to the extensive teachings of the specification that support enablement, which requires that the application teach how to make and use the invention.

First, the specification does teach one of skill in the art to how to <u>make</u> the invention (see, *e.g.*, the specification at page 13, line 26 to page 15, line 30 and Example 1, page 32, line 13 to page 33, line 2). Furthermore the specification teaches one of skill in the art how to <u>use</u> the invention (see, *e.g.*, the specification at page 20, line 10 to page 21, line 30 (describing pharmaceutical formulations), page 21, line 32 to page 24, line 8 (describing therapeutically acceptable methods and amounts), page 24, lines 10-20 (describing methods of administration), and page 24, line 22 to page 26, line 24 (describing therapeutic formulations and pharmaceutical compositions)). Accordingly, the specification has fully enabled the invention as claimed because it teaches how to make and use the invention without undue experimentation.

Applicants further note that the specification provides numerous examples supporting enablement. For example, the oligonucleotides of the invention have been tested extensively *in*

vitro in a variety of cell types. These *in vitro* experiments were performed by analyzing the ability of the claimed antisense oligonucleotides to inhibit existing infections and to protect against infection in MT-4 cells (page 19, lines 18-25). The results of these experiments are shown in Figures 1 and 2. Additional *in vitro* experiments include an analysis of the preclinical range of anti-HIV activity of various oligonucleotides of the invention (page 26, line 26 to page 30, line 8), and an analysis of toxicity in fresh human peripheral blood mononuclear cells (page 30, lines 10-28). Several of these experiments are also detailed in the Examples 7 and 8 (page 42, line 13 to page 47, line 27), which show the anti-HIV activity of the claimed antisense oligonucleotides in fresh human peripheral blood lymphocytes and fresh human monocyte-macrophages as well as inhibition of acute infection of MT-4 cells

Additionally, Applicants respectfully emphasize that these *in vitro* results support enablement of the claimed *in vivo* methods. M.P.E.P § 2164.02 states:

> [a]n in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. . . . In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.

This section further states that a "rigorous or an invariable exact correlation is not required . .. ."

Still further, the specification provides extensive support for, and evidence of, the efficacy of the invention *in vivo*. For example, at page 31, line 23 to page 32, line 5, and Example 9 (page 47, line 29 to page 52, line 23) of the instant patent application provides a description of *in vivo* testing methods to evaluate the presence of the claimed antisense oligonucleotides absorbed by the body after oral administration. In addition, the specification, at page 30, line 30 to page 31, line 21, teaches that oligonucleotides of the invention, when examined *in vivo*, were found to be intravenously and orally bioavailable in both rats and monkeys. Indeed, the specification, as amended, states at page 30, line 30 to page 31, line 4 that "the bioavailability of Oligo 12 was examined in vivo and was found to be intravenously and orally bioavailable to rats and monkeys after a single dose. . . . [and] synthetic oligonucleotides systemically administered to pregnant murine females were found to cross the placenta and be

available in the blood of embryos in utero." Furthermore, the specification at page 31, lines 14-21 states that an oligonucleotide of the invention "was found to be absorbed through the gatstrointestinal tract and accumulated in various organs and tissues" following intravenous or oral administration.

Finally, in support of enablement of the claimed invention, Applicants have submitted Exhibits B and C, discussed above, which evidence the efficacy of the claimed method of treating HIV-1 *in vivo* in various human clinical trials.

Applicants also note, for the record, that claims 34-36 are directed to a method of inhibiting HIV-1 or HIV-2 infection in a cell. As discussed above, Examples 7 and 8 (page 42, line 13 to page 47, line 27) show anti-HIV activity in fresh human peripheral blood lymphocytes and fresh human monocyte-macrophages as well as inhibition of acute infection of MT-4 cells. Accordingly, these claims have been directly enabled by several of the working examples in the specification as discussed above.

In conclusion, Applicants assert that the claimed invention is enabled because of the relative narrowness of the claims, the state of development of the claimed invention, and the extensive guidance provided in the specification showing how to make and use the invention without undue experimentation. Accordingly, reconsideration and withdrawal of the enablement rejection is respectfully requested.

Rejection under 35 U.S.C. §102

Claim 1 has been rejected under 35 U.S.C. §102 (a) or 102(e) as being anticipated by Cohen *et al.* In particular, the Office Action cites SEQ ID NO:7 of Cohen *et al.* as being relevant in this regard.

Applicants respectfully traverse this rejection for the reasons the following reasons.

Applicants respectfully assert that the Cohen *et al.* reference does not provide an enabling disclosure of the instant claimed invention because the Cohen *et al.* reference teaches materials and methods for separating modified and unmodified oligonucleotide analogs using, as one

example, the cited SEQ ID NO:7. Notably, the Cohen *et al.* reference fails to teach a specific use of the phosphorothioate oligonucleotide described by SEQ ID NO:7. In particular, the usefulness of this sequence as an antisense oligonucleotide for treating HIV is not taught. Accordingly, Applicants respectfully assert that the mere listing of SEQ ID NO:7 does not provide an enabled, and hence anticipatory, disclosure of the claimed invention.

Notwithstanding Applicants' belief that the Cohen *et al.* reference is not enabling of the instant claimed invention, Applicants have amended independent claim 1 so as to exclude the specific sequence taught by Cohen *et al.* (*i.e.,* SEQ ID NO:4 of the instant application). Dependent claim 13, which specifically claims an oligonucleotide of SEQ ID NO:4, has, accordingly, been canceled. Applicants note that this amendment finds support throughout the application in, for example, the numerous positive recitations of SEQ ID NO:4. To this point, MPEP §2173.05(i) states "there is nothing inherently ambiguous or uncertain about a negative limitation" and that "[if] alternative elements are positively recited in the specification, they may be explicitly excluded in the claims." Citing *In re Johnson*, 558 F.2d 1008, 1019, and 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining"). Applicants therefore respectfully assert that the above amendment is proper and obviates this rejection in view of the Cohen *et al.* patent. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103

Claims 1-7 and 31-33 have been rejected under 35 U.S.C. §103(a) as being unpatentable over the Cohen *et al.* reference in view of the Baracchini *et al.* reference. In particular, the Office Action states that "Cohen *et al.* is relied upon as cited in the 102 rejection above," and that "Barachini *et al.* teach antisense oligonucleotides comprising 5' and/or 3' terminal ribonucleotides, which....comprise 2'-O-methyl groups."

Applicants respectfully assert that the amendment of independent claim 1 and cancellation of dependent claim 13, discussed above as obviating the outstanding rejection under 35 U.S.C. §102 in view of Cohen *et al.*, also obviates the instant rejection under 35 U.S.C. §103

in view of Cohen *et al.* and Baracchini *et al.* In particular, the only relevant sequence taught by Cohen *et al.* has been excluded from the claimed subject matter. Applicant therefore respectfully assert that any *prima facie* case for obviousness under 35 U.S.C. § 103 in view of Cohen *et al.* has also been obviated.

Moreover, Applicants state for the record that, notwithstanding this amendment made to claim 1 to exclude the oligonucleotide sequence taught by Cohen *et al.*, there is no motivation to combine the Cohen *et al.* reference with the Baracchini *et al.* reference. In particular, Cohen *et al.* teaches methods for separating phosphorothioate oligonucleotides. A phosphorothioate 21mer oligonucleotide having the sequence of the previously-discussed Cohen *et al.* SEQ ID NO:7 is used as an example, however no specific teaching that this oligonucleotide was an antisense oligonucleotide, in general, or its particular target and hence usefulness, in particular, is provided. Accordingly, Applicants assert that there is no *prima facie* case for obviousness in this case because there would have been no motivation to combine the antisense modifications of Barachinni *et al.* with the SEQ ID NO:7 oligonucleotide sequence taught by Cohen *et al.* to arrive at the claimed invention.

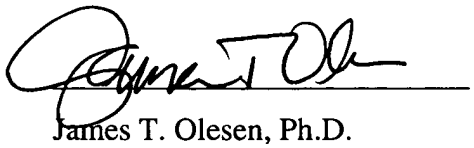
Therefore, in view of the above-described amendments and arguments, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

A Petition for a One (1) Month Extension of Time, and authorization of payment of the corresponding fee accompanies this Response. Please charge any additional fees or refund any overpayment to Deposit Account No. 08-0219.

Respectfully submitted,



James T. Olesen, Ph.D.
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Date: February 2, 2004

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ISIS™
PHARMACEUTICALS

Exhibit A

Contact: Kristina Peterson
760-603-2521

PHASE II STUDY OF ANTISENSE DRUG ISIS 2302 DEMONSTRATES SIGNIFICANT AND LONG-LASTING IMPROVEMENT OF SYMPTOMS IN PATIENTS WITH ULCERATIVE COLITIS

Carlsbad, CA, October 10, 2001 – Data from a Phase II clinical trial demonstrated that the antisense drug ISIS 2302 improved symptoms of patients with active distal ulcerative colitis (UC). Patients receiving an enema formulation of ISIS 2302 experienced a dose-dependent reduction in disease activity index score (DAI) and clinical activity index score (CAI). In the trial, the median percent reduction in DAI score at the highest dose studied was highly statistically significant compared to placebo at the end of one month of dosing ($p=0.004$) and two months following cessation of dosing ($p=0.04$). Dr. S. J. H. van Deventer, Academic Medical Center, Amsterdam, Department of Gastroenterology and Hepatology, presented these study results today at the United European Gastroenterology meeting in Amsterdam. IsisPharmaceuticals, Inc. (NASDAQ: ISIP), is developing ISIS 2302, an antisense inhibitor of intercellular adhesion molecule-1 (ICAM-1), a molecule that plays a central role in inflammation.

"Based on this first clinical experience, the retention enema formulation of ISIS 2302 appears promising as a potential new treatment for ulcerative colitis," said Dr. S. J. H. van Deventer. "We observed significant activity at the higher doses studied, and the drug and method of administration were well tolerated by patients."

The Phase II randomized, placebo-controlled dose-escalation study involved 40 people with active distal UC at 11 European trial sites. Patients participating in the study had UC for an average of six years and were allowed to remain on a standard oral medication for the disease. Patients were randomized to receive 60 mL enemas containing placebo, 0.1, 0.5, 2 or 4 mg/mL of ISIS 2302 every night for one month. Patients were evaluated for improvements in DAI and CAI scores upon completion of dosing and during the five-month follow-up period.

Results showed that at the end of one month of dosing, patients who received a 4 mg/mL dose of ISIS 2302 experienced a median improvement in DAI score of 73%, compared to a 23% improvement for placebo patients ($p=0.004$). The median CAI score of these patients improved as well, 58% for drug-treated patients versus 32% for placebo. These median improvements in DAI and CAI scores (73% and 58%, respectively) were maintained at month three and month six of the study. Two patients in this dosing group experienced full endoscopic remission at the end of the one month dosing period. No patients in the 4 mg/mL group required additional medications during the entire six month trial period, while 50% of the placebo patients required new medications to control their symptoms.

-more-

"We are very encouraged by the favorable results we've observed in this trial of ISIS 2302 in ulcerative colitis, particularly with the durability of response after a single month of dosing," said F. Andrew Dorr, M.D., Isis' Vice President and Chief Medical Officer. "These patients currently have few alternatives to surgery to control their disease. We will continue to refine the dosing schedule and evaluate the market potential of this new product opportunity."

ISIS 2302 is an antisense inhibitor of ICAM-1, a molecule that plays a key role in a wide range of inflammatory and autoimmune conditions such as UC. ICAM-1 is part of a family of molecules, the cellular adhesion molecules, that can be found on the surface of virtually every cell in the body, including cells that line the colon. It is involved in the production of immune factors that cause the inflammatory response in UC. ISIS 2302 is also being studied in Crohn's disease and a topical formulation for psoriasis.

According to the Crohn's and Colitis Foundation of America, UC is an inflammatory disease of the colon, the large intestine, which is characterized by inflammation and ulceration of the innermost lining of the colon. Symptoms characteristically include diarrhea, rectal bleeding and abdominal pain. UC differs from another inflammatory bowel disease, Crohn's disease, as it only affects the colon. An estimated 500,000 Americans have UC.

Isis will conduct a live webcast conference call to discuss this release on Wednesday, October 10 at 10:30 AM Eastern time. To participate over the internet, go to www.isip.com. A replay of the webcast will be available at this address for up to 90 days.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. Isis has 12 antisense products in its development pipeline with two in late-stage development and six in Phase II human clinical trials. Isis' GeneTrove™ division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services and access to an extensive gene function database. Ibis Therapeutics™ is a division focused on the discovery of small molecule drugs that bind to RNA. Isis has a broad patent estate as the owner or exclusive licensee of more than 800 issued patents worldwide.

This press release contains forward-looking statements concerning the clinical development of ISIS 2302, its prospects as a treatment for ulcerative colitis and the potential of Isis' drug discovery program. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and financing such activities. Actual results could differ materially from those projected in this release. As a result, the reader is cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail in the Registration Statement on Form S-3 filed October 9, 2001 with the U.S. Securities and Exchange Commission, copies of which are available from the company.

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GeneTrove™ and Ibis Therapeutics™ are trademarks of Isis Pharmaceuticals, Inc.

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Exhibit B

Drug Development

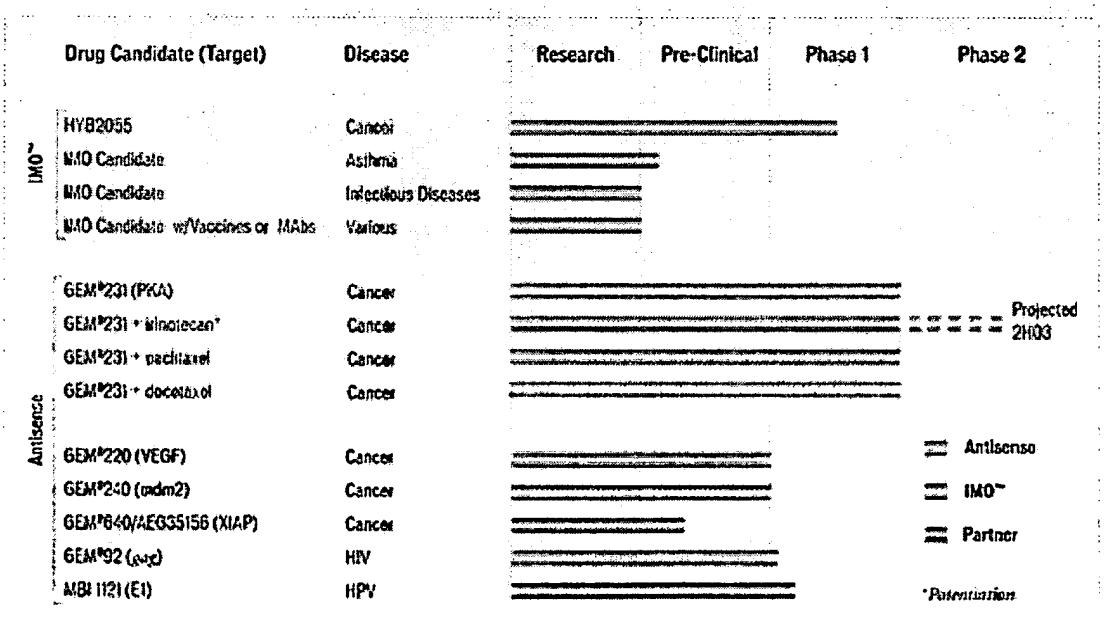
Clinical programs

As a pioneering company in antisense technology, Hybridon has developed extensive experience, both in preclinical and clinical studies, involving the systemic administration of antisense drug candidates. Results of early trials in man indicated that first generation antisense agents produced certain side effects that were not anticipated from preclinical studies. These results prompted Hybridon further to modify chemically its antisense agents, leading to the identification of a series of 2nd generation antisense agents with improved pharmaceutical properties. These advanced chemistry antisense agents have increased metabolic stability (providing the potential for administration by the oral route), enhanced potency, and an improved side effect profile.

All of Hybridon's antisense drug candidates are 2nd generation, antisense agents. Hybridon's initial product focus is in the therapeutic areas of oncology and viral disease.

In the area of immune modulation, Hybridon has begun the clinical development of its lead IMO™ compound, HYB2055. This drug candidate is a synthetic compound with advanced chemical modifications which Hybridon believes may offer advantages over earlier CpG oligos. Based on Hybridon's expertise in synthetic DNA chemistry and an understanding of the structure-activity relationship by which IMO™ compounds can modulate the vertebrate immune system, HYB2055 is only the first in what Hybridon expects to be a series of IMO™ compounds, each of which can be fine-tuned with to desired potency, specificity and duration of action.

Hybridon's Drug Development Product Pipeline



Hybridon has three drug candidates in the clinical phase of development.

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conducted at Vanderbilt University Medical Center and the University of Chicago Medical Center. Hybridon plans to complete this trial in 2003.

GEM®231 is a 2nd generation antisense compound for treating solid tumor cancers. We chose to evaluate the combination of GEM®231 and Camptosar based on promising preclinical data relating to this combination as a treatment of solid tumor cancers.

In the clinical trial, we are evaluating the safety of GEM231 and Camptosar in combination and measuring the presence of extra-cellular PKA, or ECPKA, in blood as a biomarker for GEM231 antisense activity. A biomarker is a biological parameter monitored as a possible indicator of drug activity.

GEM®231 is designed to inhibit protein kinase A, or PKA. PKA is a protein that plays a key role in the control of the growth and differentiation of mammalian cells. Levels of PKA have been shown to be increased in the cells of many human cancers, and high levels of PKA have been shown to correlate with unfavorable clinical outcomes in patients with breast, colon and ovarian cancers.

We previously conducted other phase 1/2 clinical trials of GEM®231, both as a monotherapy and in combination with other marketed chemotherapeutics. We believe that these trials involved the first systemic administration of a 2nd generation antisense compound to oncology patients. In December 2002, we completed a phase 1/2 study of 14 patients with solid tumors undergoing treatment with GEM®231 as a monotherapy. In the study, ECPKA was monitored for each patient before and during the treatment as a biomarker for GEM®231 activity. Results of the study showed a decrease in ECPKA in patients.

In the phase 1/2 trial of GEM®231 as a monotherapy and in our other trials of GEM®231, we also evaluated the safety of GEM®231 in multiple doses in oncology patients. These trials explored the maximum tolerated dose of GEM®231 for both single doses and multiple doses. In the trials, GEM®231 was generally well tolerated. Even in high doses, GEM®231 did not show some of the side effects normally associated with most current cancer treatments or with 1st generation antisense compounds.

GEM®92

Status: The initial single dose phase 1 study of GEM®92 orally at three dose levels and by injection showed excellent safety results and successfully confirmed in humans oral delivery of 2nd generation antisense agents. Hybridon is evaluating the market opportunity for GEM®92 in view of the current effectiveness of HAART therapies in treating HIV. We may recommence our development efforts if and when viral resistance to existing therapies results in a need for a new approach to HIV treatment.

Based on the clinical experience we gained with GEM®91, our 1st generation antisense compound that also targeted the same region of HIV-1, we created chemical modifications to improve the side effects profile and to enhance the stability of the compound. In 1997, we conducted a phase 1 study in the United Kingdom to investigate the safety and pharmacokinetics of single doses of GEM®92, given at three different dose levels by the oral route and one does level as a 2-hour intravenous infusion. All doses given in the study were well tolerated by the patients. Further, GEM®92 was detected in the blood after both oral dosing and injection, suggesting that GEM®92 could be developed as an oral drug. We believe both that the medicinal approach and genetic target for GEM®92 are unique in that no antisense drug has been approved for the treatment of AIDS, and no other drug has the same target on the HIV-1 genome.

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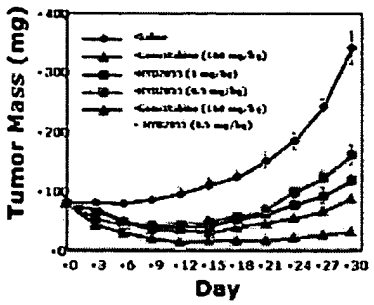
Immunomodulatory Oligonucleotides (IMO™)

HYB2055

Anti-Tumor* Activity of HYB2055



* Human prostate cancer PC-3 in male nude mice; IMO™ Treatment Day 1, 3, 5/week

immunologic activity and pharmacokinetics of HYB2055 in healthy individuals. In May 2003, a phase 1 clinical trial was initiated at Georgetown University's Lombardi Cancer Center in cancer patients with malignant solid tumors.

HYB2055 is the lead compound in Hybridon's IMO™ program. HYB2055 is an immune stimulator. Preclinical data in animal and human cells has shown HYB2055 activates cells of the immune system to secrete a number of effector molecules, or cytokines. In animals bearing various human cancer xenographs, HYB2055 shows potent anti-tumor activity.

In addition to cancer, we believe the IMO™ compounds used in HYB2055 could also have use as a monotherapy for treatment of allergic asthma and other allergies and infectious diseases. IMO™ compounds may also be useful as co-factors in combination therapeutic agents with vaccines, monoclonal antibodies (MAbs), peptides, chemotherapeutic agents, allergens and antigens.

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Collaborations

MG98

Status: Phase 1 dose-escalation clinical trials of MG98 have been completed. Phase 2 clinical trials have been initiated. For further updates, visit www.methylgene.com.

Work on antisense inhibitors of DNA methyl transferase began as a Hybridon research project, in collaboration with Dr. Moshe Szyf of McGill University. The enzyme, DNA methyltransferase, is considered to be a key regulator responsible for maintaining aberrant DNA methylation in human cancer cells. The first drug candidate developed by MethylGene to enter clinical development is MG98, a 2nd generation antisense agent that inhibits the production of DNA methyl transferase.

MethylGene Inc was formed in 1996 as a Hybridon spinout company. In April 2001, Hybridon sold its equity interest in MethylGene.

MBI 1121 (FORMERLY ORI 1001)

Status: MBI 1121 is currently in phase 1. For further updates, visit www.mbiotech.com.

MBI1121 is a 2nd generation antisense analog that targets the E1 protein of human papillomavirus (HPV). The E1 protein is a highly conserved element across a number of HPV types and has an essential role in viral replication. In September 2002, Micrologix acquired ORI 1001, which was formerly owned, and being developed by Origenix Technologies Inc. for the treatment of diseases associated with (HPV) such as external genital warts. In conjunction with the acquisition of this HPV molecule, Micrologix entered into a collaboration with Hybridon for exclusive rights for a patent covering HPV antisense oligonucleotides for use against the HPV genome as well as the non-exclusive rights to a portfolio of antisense oligonucleotide chemistry patents.

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HIV Can Be Treated

Exhibit C

Oligonucleotides

First-generation HIV-Antisense Oligonucleotide Trials Halted

On Friday, July 28, 1997, Hybridon Inc., of Cambridge, Massachusetts, announced that is halting development of GEM91, its first-generation antisense oligonucleotide directed against the HIV gag gene, because of platelet depletion in trial patients. The company will focus efforts on GEM92, a second-generation antisense compound, which also targets the gag site of the viral genome.

Earlier trials indicated that GEM91 significantly reduced viremia in HIV-positive patients treated for up to eight days. However, in the latest Phase IIb trial, 3 of 9 patients with advanced HIV infection experienced a decrease in platelet count after ten days of treatment.

This finding led to the decision to halt development of the compound. In a company communication, Hybridon VP Dr. Russell Martin said, "...even if efficacy could be demonstrated, the results of this Phase II clinical trial indicated that chronic therapy for advanced HIV patients with GEM91 in combination with other antiretrovirals likely would require periodic interruption of drug administration."

The second-generation antisense products being developed by Hybridon, unlike the first-generation phosphorothioates, are mixed backbone oligonucleotides. "We believe these second generation oligonucleotides will have a substantially greater therapeutic index," said Hybridon Chairman E. Andrews Grinstead. He added, "The growing population of AIDS patients who...develop resistance to triple combination therapy may be helped by GEM92."

GEM92 is expected to enter clinical trials in October. So far, animal studies show that it causes substantially fewer platelet and liver changes than GEM91, and that it has the potential for oral administration. Dr. Martin said he hopes GEM92 will have "...increased potency, reduced frequency of dosing administration and an improved safety profile, as compared to first generation antisense compounds."

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